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## UNITED STATES PATENT AND TRADEMARK OFFICE

Application No. : 10/643,160  
First Named Inventor : Dmitry M. Rudkevich  
Filing Date : August 18, 2003  
Title : METHODS, SYSTEMS AND USES FOR CALIXARENES  
Group Art Unit : 1723  
Examiner : Joseph W. Drodge  
Confirmation No. : 3568

## DECLARATION UNDER 37 § CFR 1.131

I, Dmitry M. Rudkevich, declare that:

1. I am the named inventor in the above-identified U.S. Application No. 10/643,160 filed August 18, 2003.

2. I conceived and reduced to practice in the United States of America the invention as shown and described in the above-identified application prior to the date of February 13, 2003, the date of publication of Zyryanov et al. (JACS 2003;125:2997-3007).

3. Prior to February 13, 2003, I prepared a document attached as **EXHIBIT A** that represents an example of the reduction to tangible form of my mental concept of the invention as shown and claimed in the above-identified application.

4. **EXHIBIT A** is a document to Professor Stang of the Department of Chemistry at the University of Utah along with a copy of an online submission of a manuscript entitled "Sensing and Fixation of  $\text{NO}_2/\text{N}_2\text{O}_4$  by Calix[4]Arenes" that describes compositions of the claimed invention and properties and methods of making the claimed invention. In particular, the Introduction on pages 2-3 of the Exhibit A manuscript corresponds to paragraphs [0002]-[0003] and [0006]-[0009] of the above-identified application and Scheme 1 on page 5 of the Exhibit A manuscript corresponds to Scheme 1 on page 15 of the of the above-identified application and teaches and shows a calix[4]arene compound capable of forming a complex with at least one  $\text{NO}^+$  cation, wherein a detectable charge-transfer reaction occurs between the  $\text{NO}^+$  cation and the calix[4]arene as set forth in the claims now pending.

5. Prior to February 13, 2003, I disclosed and reported the invention to Professor Stang of the Department of Chemistry at the University of Utah as set forth in **EXHIBIT A**.

6. Pursuant to the evidence set forth in **EXHIBIT A**, I reduced to practice the invention as described and claimed in the above-identified application in the United States of America prior to February 13, 2003.

7. It is my belief that the above-cited facts, as supported by **EXHIBIT A**, provide clear evidence of my conception and actual reduction to practice of the invention described and claimed in the above-identified application prior to February 13, 2003.

8. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.



Dmitry M. Rudkevich

02/22/06

Date

Exhibit A



UNIVERSITY OF TEXAS  
AT ARLINGTON

Dr. Dmitry M. Rudkevich  
Assistant Professor of Organic Chemistry  
Dept. of Chemistry & Biochemistry  
The University of Texas at Arlington  
Box 19065, Arlington, TX 76019  
Phone: 817 272 5245  
FAX: 817 272 3808  
E-mail: [rudkevich@uta.edu](mailto:rudkevich@uta.edu)

**To:** Prof. Peter J. Stang, Editor  
Department of Chemistry,  
University of Utah,  
315 South 1400 East, RM 2020  
Salt Lake City, Utah 84112-0850

**Dear Prof. Stang,**

This online submission offers the manuscript from our laboratory for your kind consideration as a full paper in the *Journal of the American Chemical Society*.

**Title:** Sensing and Fixation of  $\text{NO}_2/\text{N}_2\text{O}_4$  by Calix[4]Arenes

**Corresponding author:** Dmitry M. Rudkevich

In our laboratory, we employ principles of molecular recognition for gas complexation, sensing and fixation. The above manuscript presents the experimental results on quite unexpected interaction between  $\text{NO}_2$  and simple calixarenes.

Nitrogen dioxide ( $\text{NO}_2$ ) is a major component of so-called  $\text{NO}_x$  gases. These are toxic atmospheric pollutants and are also involved in the formation of ground-level ozone, participate in global warming, and also form toxic chemicals, nitrate particles and acid rain/aerosols.  $\text{NO}_x$  aggressively participate in various nitrosation processes in biological tissues. The pathophysiological significance of  $\text{NO}_x$  derives from their ability to generate mutagenic nitroso- and further diazo peptides, to produce carcinogenic nitrosoamines, and to nitrosate and further deaminate DNA nucleobases. According to The United States Environmental Protection Agency, national emissions of  $\text{NO}_x$  have increased over the past 20 years by 4%, which is rather alarming.

Extensive NO<sub>2</sub> circulation in the atmosphere requires not only its systematic monitoring but also necessitates the development of improved methods of the NO<sub>2</sub> fixation and utilization.

We found, that calixarenes react with NO<sub>2</sub> to form stable nitrosonium (NO<sup>+</sup>) complexes. These calixarene-NO<sup>+</sup> complexes are deeply colored and can dissociate upon addition of water. Thus, calixarenes conveniently transmit the information about NO<sub>2</sub> binding via visible light signals. The described charge-transfer interactions are unique for NO<sub>2</sub> and would guaranty its detection in the presence of such gases as H<sub>2</sub>O, O<sub>2</sub>, HCl, SO<sub>x</sub>, NH<sub>3</sub>, and even NO. Furthermore, these complexes can be utilized for the NO<sup>+</sup> transfer processes and nitrosation reactions. Accordingly, our results offer a novel process of NO<sub>2</sub> visual sensing and chemical utilization and may also lead towards novel, supramolecular NO<sub>2</sub>-storing materials.

The figures should be presented in color.

Suggested Associate Editor: **Dr. Eric V. Anslyn**, The University of Texas at Austin.

**Suggested Reviewers:**

1. **Prof. David N. Reinhoudt**, Laboratory of Supramolecular Chemistry and Technology, University of Twente, P. O. Box 217, 7500 AE Enschede, The Netherlands  
e-mail (direct): d.n.reinhoudt@ct.utwente.nl  
e-mail (secretary): 1. C.E.vanderPloeg@ct.utwente.nl  
2. smct@ct.utwente.nl
2. **Prof. François Diederich**, Organic Chemistry Laboratory, ETH Zentrum, CH-8092 Zuerich, Switzerland.  
Phone: +41-1-632 2992  
Fax: +41-1-632 1109  
e-mail : diderich@org.chem.ethz.ch
3. **Prof. Bradley D. Smith**, Department of Chemistry and Biochemistry, University of Notre Dame, 251 Nieuwland Science Hall, Notre Dame, IN 46556-5670.  
Phone: (219) 631-8632  
FAX: (219) 631-6652  
e-mail: [smith.115@nd.edu](mailto:smith.115@nd.edu)

4. **Prof. George B. Richter-Addo**, Department of Chemistry and Biochemistry, University of Oklahoma, 620 Parrington Oval, Room 208, Norman, Oklahoma 73019-3051.  
Phone: 405-325-6401  
e-mail: [grichteraddo@ou.edu](mailto:grichteraddo@ou.edu)
5. **Prof. Jonathan L. Sessler**, Department of Chemistry and Biochemistry, The University of Texas at Austin  
Austin, TX 78712. Campus Code A5300  
e-mail: [sessler@mail.utexas.edu](mailto:sessler@mail.utexas.edu)
6. **Prof. Jay S. Siegel**, Department of Chemistry & Biochemistry, University of California San Diego, 9500 Gilman Drive, MC 0358 La Jolla, CA 92093-0358.  
Phone: (858) 534-5659  
FAX: (858) 822-0386  
e-mail: [jssiegel@ucsd.edu](mailto:jssiegel@ucsd.edu)
7. **Prof. Michael Lattman**, Department of Chemistry, Southern Methodist University, P.O.Box 750314, Dallas, TX 75275-0314.  
Phone: (214) 768-2467  
FAX: (214) 768-4089  
e-mail: [mlattman@mail.smu.edu](mailto:mlattman@mail.smu.edu)
8. **Prof. Jerry L. Atwood**, Department of Chemistry, University of Missouri-Columbia, 601 South College Ave., Columbia, MO 65211  
Phone: (573) 882-8374;  
e-mail: [AtwoodJ@missouri.edu](mailto:AtwoodJ@missouri.edu)

**Potential Conflict of Interest:** We kindly ask not to include Prof. J. K. Kochi of the University of Houston into the referee's list.

I very much hope, that you, the Associate Editor, and your highly respected referees will like our work and support the publication.

Sincerely,

Dr. Dmitry M. Rudkevich



# Sensing and Fixation of NO<sub>2</sub>/N<sub>2</sub>O<sub>4</sub> by Calix[4]Arenes

Grigory V. Zyryanov, Yanlong Kang, and Dmitry M. Rudkevich\*

*Contribution from the Department of Chemistry and Biochemistry, University of Texas at Arlington, P. O. Box 19065, Arlington, TX 76019*

**Abstract:** An approach towards visual detection and chemical utilization of NO<sub>2</sub>/N<sub>2</sub>O<sub>4</sub> is proposed, which employs simple calix[4]arenes. Exposure of tetra-*O*-alkylated calix[4]arenes **1,2** and **5**, possessing either a *cone* or a *1,3-alternate* conformation, to NO<sub>2</sub>/N<sub>2</sub>O<sub>4</sub>, both in chloroform solution and in the solid state, results in deeply colored calixarene-nitrosonium (NO<sup>+</sup>) complexes. In the presence of a Lewis acid, such as SnCl<sub>4</sub>, stable calixarene-NO<sup>+</sup> complexes **7** and **8** were isolated in a quantitative yield and characterized by UVvis, FTIR, high-resolution <sup>1</sup>H NMR spectroscopy and elemental analysis. NO<sup>+</sup> is found encapsulated within the calixarene cavity, and stable charge-transfer complexes result with  $K_{\text{ass}} > 10^6 \text{ M}^{-1}$  (CDCl<sub>3</sub>). The NO<sup>+</sup> encapsulation was also demonstrated in titration experiments with calixarenes **1,2** and **5** and commercially available NO<sup>+</sup>SbF<sub>6</sub><sup>-</sup> salt in chloroform. The complexation process is reversible, and the complexes dissociate upon addition of water and alcohol, recovering the parent calixarenes. Attachment of functionalized calix[4]arenes to silica gel was demonstrated, which afforded a solid material **15** capable of visual detection and entrapment of NO<sub>2</sub>/N<sub>2</sub>O<sub>4</sub>. Calixarene-NO<sup>+</sup> complexes can be utilized for the NO<sup>+</sup> transfer processes and nitrosation reactions. The NO<sup>+</sup> guest transfer between two calixarene containers **2** and **5** was achieved and studied by UVvis and <sup>1</sup>H NMR spectroscopy. Chemical fixation of NO<sub>2</sub>/N<sub>2</sub>O<sub>4</sub> was demonstrated through their quantitative transformation into the calixarene-NO<sup>+</sup> complex and its use as a nitrosonium transfer agent in the synthesis of *N*-nitrosoamides. These results may lead towards novel nitrogen oxides storing materials.

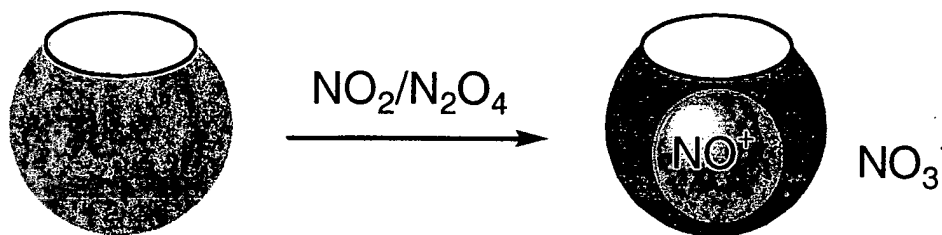
# Sensing and Fixation of $\text{NO}_2$ by Calix[4]Arenes

Grigory V. Zyryanov, Yanlong Kang, and Dmitry M. Rudkevich\*

*Contribution from the Department of Chemistry and Biochemistry, University of Texas at Arlington, P. O. Box 19065, Arlington, TX 76019*

## Introduction

Nitrogen dioxide ( $\text{NO}_2$ ) is a major component of so-called  $\text{NO}_x$  gases.<sup>1,2</sup>  $\text{NO}_x$  is the term used to describe the sum of nitric oxide ( $\text{NO}$ ),  $\text{NO}_2$  and other oxides of nitrogen. These are toxic atmospheric pollutants derived from fossil fuel combustion, power plants, and large-scale industrial processes.  $\text{NO}_x$  are involved in the formation of ground-level ozone, participate in global warming, and also form toxic chemicals, nitrate particles and acid rain/aerosols.  $\text{NO}_x$  are aggressively involved in various nitrosation processes in biological tissues. Free radical  $\text{NO}$  rapidly reacts with oxygen, producing  $\text{N}_2\text{O}_3$  (e.g.,  $\text{NO}\cdot\text{NO}_2$ ) and  $\text{NO}_2/\text{N}_2\text{O}_4$ . These are powerful nitrosating agents, both in the gas phase and in solution. The pathophysiological significance of  $\text{NO}_x$  derives from their ability to generate mutagenic nitrosopeptides and further diazopeptides, to produce carcinogenic nitrosoamines, and to nitrosate and further deaminate DNA nucleobases. According to The United States Environmental Protection Agency,<sup>1</sup> national emissions of  $\text{NO}_x$  have increased over the past 20 years by 4%. Tolerable levels of  $\text{NO}_x$  are  $\leq 5$  ppm.



**Figure 1.** Chemical fixation of  $\text{NO}_2/\text{N}_2\text{O}_4$  with calix[4]arenes, a cartoon representation. Formation of encapsulated nitrosonium complexes.

Extensive NO<sub>2</sub> circulation in the atmosphere requires not only its systematic monitoring but also necessitates the development of improved methods of the NO<sub>2</sub> fixation and utilization. Here, we describe host-guest complexes, formed upon interaction between NO<sub>2</sub> and simple calix[4]arenes (Figure 1).<sup>3</sup> We found, that *a*) calixarenes react with NO<sub>2</sub> to form stable nitrosonium (NO<sup>+</sup>) complexes, *b*) these calixarene-NO<sup>+</sup> complexes are deeply colored and can dissociate/bleach upon addition of water, and *c*) these complexes can be utilized for the NO<sup>+</sup> transfer processes and nitrosation reactions. Accordingly, our results offer a novel process of NO<sub>2</sub> visual sensing and chemical utilization and may also lead towards novel, supramolecular NO<sub>2</sub>-storing materials.

## Results and Discussion

**Rationale and Design.** Calix[4]arenes are popular building blocks in molecular recognition and they are widely used in the construction of molecular containers – cavitands, (hemi)carcerands, and capsules.<sup>4</sup> *Cone*-shaped calix[4]arenes are ~4 Å deep and ~7 Å in diameter at the upper rim. Tetra-*O*-alkylated *cone* calix[4]arenes exist in the pinched C<sub>2v</sub> symmetrical conformation, with two opposite aromatic rings almost parallel and situated ~5 Å apart, and two others flattened. This conformation is more preferable than the perfect cone C<sub>4v</sub> conformation. Usually, the interconversion between two C<sub>2v</sub> structures is fast on the NMR time scale.<sup>5</sup> Calix[4]arenes in a *1,3-alternate* conformation are much more rigid and possess a cylindrical inner tunnel, defined by two cofacial pairs of aromatic rings oriented orthogonal along the cavity axis. According to the number of X-ray studies, this tunnel is ~5-6 Å in diameter.<sup>6</sup>

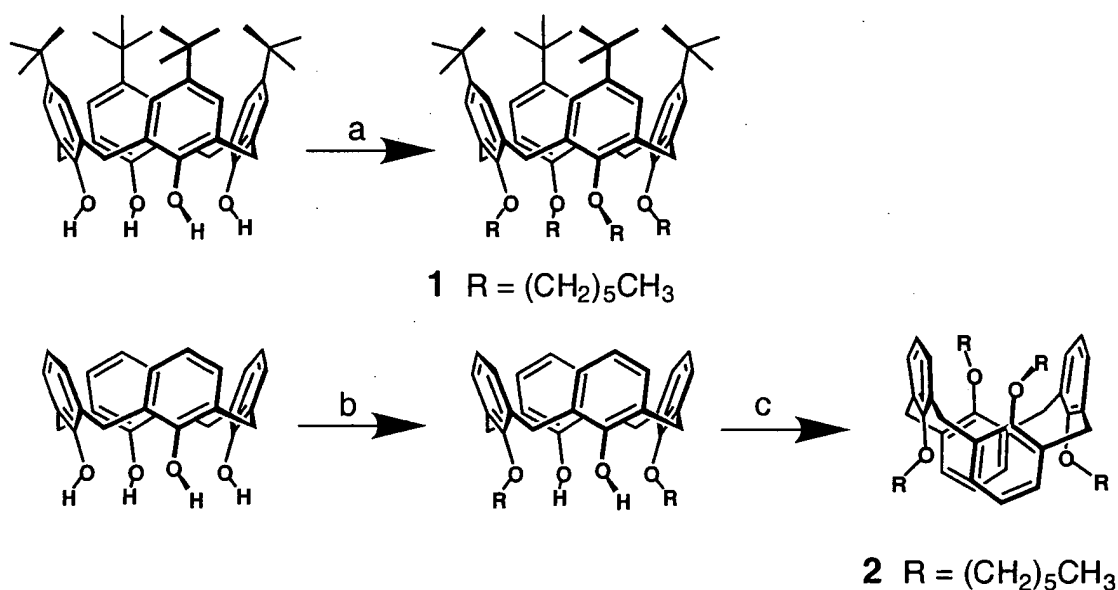
Complexes of calix[4]arenes with neutral molecules are weak. The cavities are obviously too small and they also lack additional binding sites. In most of the crystal structures of the inclusion complexes of calixarenes, the guest molecule is positioned not inside but roughly above the plane defined by the upper carbon atoms of the cyclic polyaromatic skeleton. On the other hand, cations

are known to more strongly interact with the calixarene  $\pi$ -surface. Ammonium ions and metal cations were found complexed within the cone-shaped cavities.<sup>7</sup> *1,3-Alternates*, functionalized with appropriate binding sites on the phenol oxygens, bind metal cations -  $\text{Na}^+$ ,  $\text{K}^+$ , and  $\text{Ag}^+$  - both with “hard” oxygens and “soft”  $\pi$ -basic aromatic rings.<sup>8</sup> Recently, Kochi, Rathore and co-workers described very stable complexes between calix[4]arenes and nitrosonium ( $\text{NO}^+$ ) cation, both in solution and in the solid state.<sup>9</sup> The  $\text{NO}^+$  cation was found *encapsulated* within the calixarene cavity (X-ray analysis), and strong charge-transfer interactions with the  $\pi$ -surface of calixarene positioned the guest in between the cofacial aromatic rings at a distance 2.4 Å, which is much shorter than the typical van der Waals contact (3.2 Å).

$\text{NO}_2$  is a paramagnetic gas since it has an unpaired electron on the nitrogen. It has an intense brown-orange color. Reacting with itself, it forms the colorless dimer, dinitrogen tetroxide ( $\text{N}_2\text{O}_4$ ).<sup>10</sup> The N-N bond in  $\text{N}_2\text{O}_4$  is quite weak, and as the temperature is raised it rapidly dissociates back to  $\text{NO}_2$ . The position of the equilibrium between the two compounds and the color of the system vary with temperature. Below  $-21^\circ\text{C}$ , only pure, solid  $\text{N}_2\text{O}_4$  is present. Above  $140^\circ\text{C}$  the system is 100%  $\text{NO}_2$ . The *dynamic* interconversion between  $\text{NO}_2$  and  $\text{N}_2\text{O}_4$  makes it impossible to study either of these species alone. Of particular importance for us,  $\text{N}_2\text{O}_4$  may disproportionate to ionic  $\text{NO}^+\text{NO}_3^-$  upon reacting with aromatic compounds.<sup>11</sup>

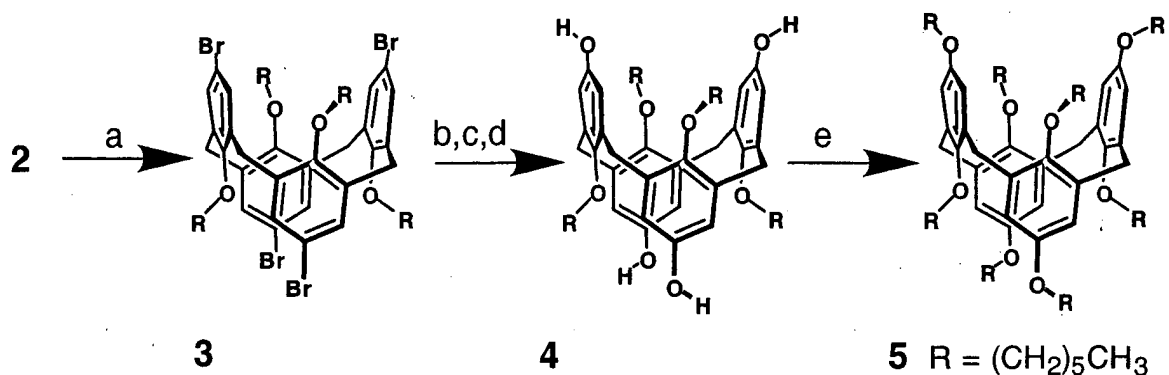
Combining these features of  $\text{NO}_2/\text{N}_2\text{O}_4$  with unique complexing abilities of calix[4]arenes, we expected that interactions between them might lead to calixarene-nitrosonium complexes. Below, we describe the sequence of experiments, elaborating this idea, and also the chemical consequences, that follow.

**Synthesis.** Calix[4]arenes **1**<sup>12</sup> and **2**, possessing a *cone* and a *1,3-alternate* conformation, respectively, were synthesized through *O*-alkylation of the corresponding parent calix[4]arenes with *n*-hexylbromide (Scheme 1). In the synthesis of **1**, NaH was employed as a base in hot DMF. Preparation of **2** includes the two-step alkylation of de-*t*-butylated calix[4]arene with *n*-hexyl bromide, using successively K<sub>2</sub>CO<sub>3</sub> and then Cs<sub>2</sub>CO<sub>3</sub> in boiling MeCN.<sup>13</sup>



**Scheme 1.** a) *n*-hexyl bromide, NaH, DMF, 70 °C, 24 h, 75%. b) *n*-hexyl bromide, K<sub>2</sub>CO<sub>3</sub>, MeCN, 80 °C, 48 h, 84 %. c) *n*-hexyl bromide, Cs<sub>2</sub>CO<sub>3</sub>, MeCN, 80 °C, 48 h, 46%.

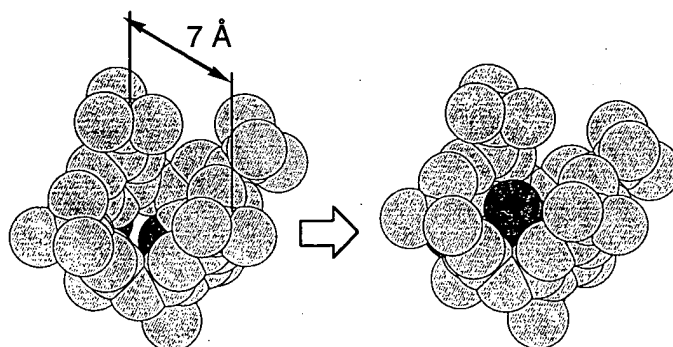
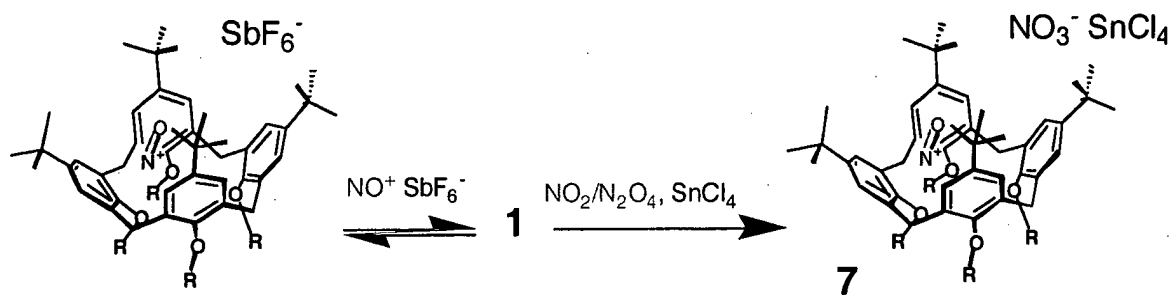
Bromination of **2** with NBS in acetone afforded tetrabromocalix[4]arene **3** in 53% yield (Scheme 2). Tetrahydroxylated *1,3-alternate* derivative **4** was obtained through bromo-lithium exchange in **3** (*n*-BuLi, THF, -78 °C), followed by treatment with B(OMe)<sub>3</sub> and oxidation with H<sub>2</sub>O<sub>2</sub> and aq NaOH (40% yield after three steps). Calixarene **4** was subsequently alkylated with *n*-hexylbromide and NaH in hot DMF to yield octahexyloxycalix[4]arene **5** in 85%.<sup>14</sup> Mesitylene derived *1,3-alternate* **6** (Figure 4) was obtained for comparison, according to the literature procedure by Pappalardo<sup>15,16</sup> and subsequent *O*-alkylation with *n*-hexylbromide.



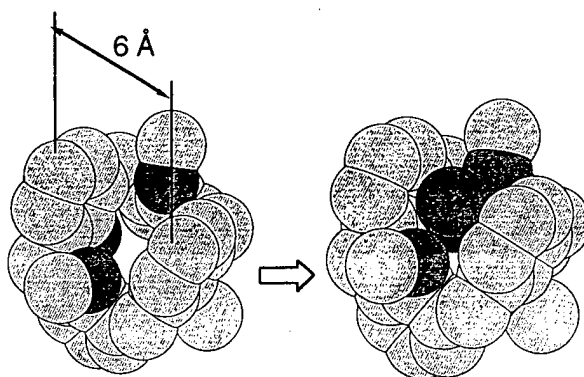
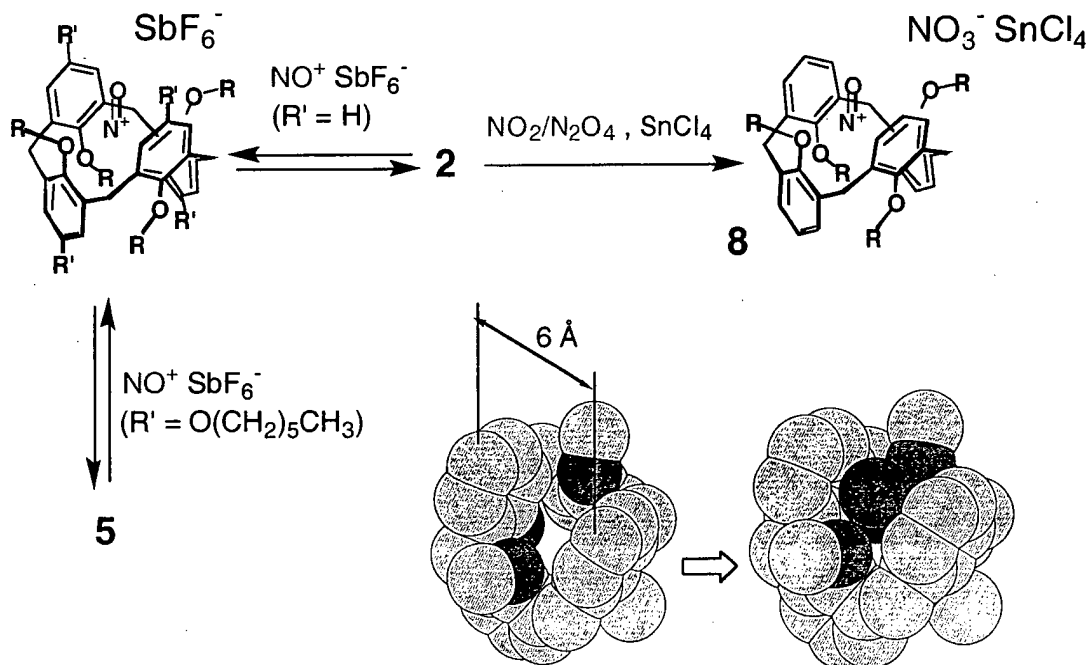
**Scheme 2.** a) NBS, acetone, rt, 48 h, 53% yield. b) *n*-BuLi (60 eq), THF, -78 °C, 0.5 h. c) B(OMe)<sub>3</sub>, -78 °C to 0 °C. d) H<sub>2</sub>O<sub>2</sub>, aq NaOH, -78 °C to 25 °C, 40%, three steps. e) *n*-hexyl bromide, NaH, DMF, 70 °C, 24 h, 85%.

**Interaction of Calix[4]arenes with NO<sub>2</sub>.** Bubbling NO<sub>2</sub> through the solutions of **1,2** and **5** in CHCl<sub>3</sub> resulted in instant, deep coloration. Solutions of **1** and **5** turned dark blue, and solution of **2** became deep purple. The UVvis spectra changed accordingly: the broad bands appeared at  $\lambda_{\text{max}} = 560, 512$  and  $600$  nm for NO<sub>2</sub>-exposed solutions of **1,2** and **5**, respectively. This is in a striking contrast to colorless solutions of **1,2** and **5**, and pale yellow solution of NO<sub>2</sub> in CHCl<sub>3</sub>, and implies a charge-transfer mechanism.

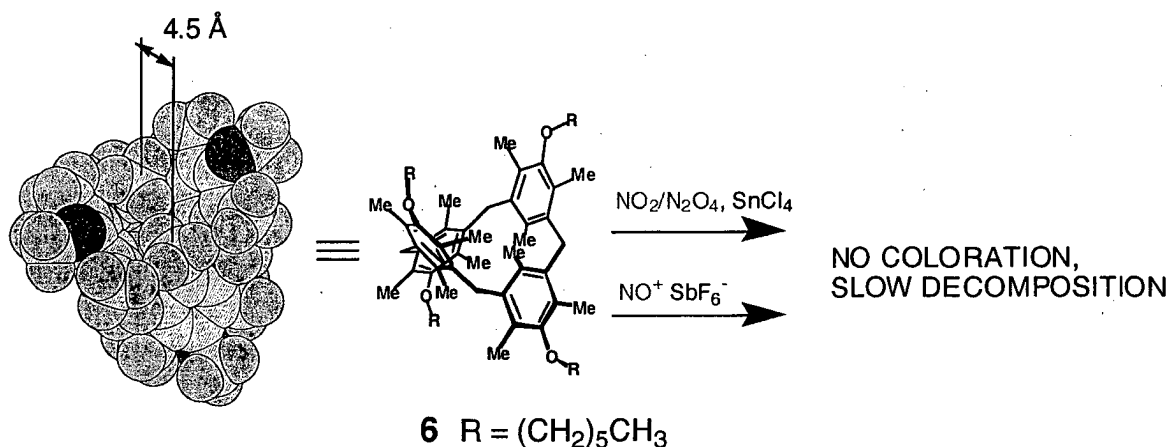
In the experiments with non-cyclic anisole (e.g., methoxybenzene), only pale coloration was observed upon exposure to NO<sub>2</sub>. Moreover, when mesitylene derived, Pappalardo's calixarene **6**, with the sterically *blocked* and conformationally much more *rigid* cavity, was tested, no coloration was observed either. In **6**, the pair of methyl groups in the *ortho*-positions to the oxygen forces the methyl groups of the adjacent aromatic rings towards each other, not only blocking an access to the cylindrical inner cavity, but also significantly rigidifying it. The same effect takes place on the other side of the calixarene **6**, which makes its interior completely hindered. These model experiments emphasize the importance of *cavities* in the described transformations and suggest the possibility of the NO<sup>+</sup> coordination inside **1,2** and **5**.



**Figure 2.** Nitrosonium complexes of calix[4]arene **1**; two methods of preparation. Below: MacroModel representation of the  $\text{NO}^+$  encapsulation process. The CH hydrogen and long alkyl chains are omitted for viewing clarity.



**Figure 3.** Nitrosonium complexes of calix[4]arene **2**; two methods of synthesis. Below: MacroModel representation of the  $\text{NO}^+$  encapsulation process. The CH hydrogen and long alkyl chains are omitted for viewing clarity.



**Figure 4.** Mesitylene-derived calixarene **6** and its space-filling MacroModel representation. The long alkyl chains are omitted for viewing clarity.

According to molecular modeling,<sup>17</sup> one  $NO^+$  cation can fit inside the cavities **1,2** and **5**, and neither bent  $NO_2$  nor bulky  $NO_3^-$  can be accommodated. Two parallel aromatic rings of a *cone* calix[4]arene participate in the  $NO^+$  complexation, and all four rings of a *1,3-alternate* calixarene are involved. In mesitylene derived calixarene **6**, no  $NO^+$  encapsulation may occur for steric reasons.

While the instant coloration implied charge-transfer between the prereactive nitrosating/nitrating species and **1,2**, and **5**, this was difficult to monitor. Interaction of  $NO_2$  with **1,2**, and **5** is very dynamic, and the initial  $^1H$  NMR analysis of the solutions gave rather complex, quickly changing pictures. The  $NO_2/N_2O_4$  mixture is known as an effective nitrosating/nitrating agent.<sup>2,10,11</sup> Not surprisingly, the  $NO_2$ -containing  $CHCl_3$  solutions of **1** and **2** bleached within 1-2 h, yielding mixtures of known *p*-nitrated calixarenes<sup>18</sup> (preparative TLC,  $^1H$  NMR). Calixarene **5**, much more activated for the electrophilic aromatic substitution, reacts with  $NO_2$  even faster - within few minutes, producing a very complex mixture of dealkylated and oxidized products.<sup>19</sup>

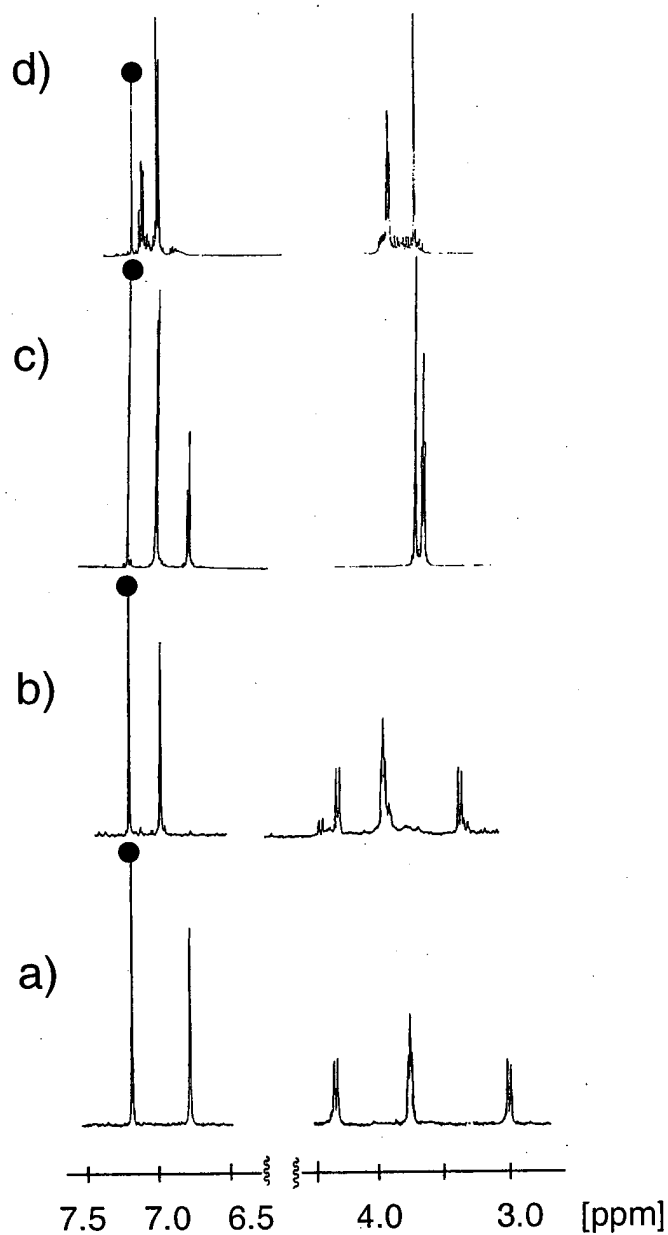
At the same time, when treated with  $SnCl_4$ , solutions of **1,2** and 2-3 equivalents  $NO_2$  did not yield the nitration products. It is known that Lewis acids stabilize arene-nitrosonium charge-transfer

complexes.<sup>10,11</sup> Precipitation with hexanes resulted in deeply colored, moisture sensitive solids, assigned to nitrosonium complexes **7** and **8** (>90% yield, Figure 2, Figure 3, Figure 4). Complex **7** is dark blue, and complex **8** is deep purple.

**Analysis and Characterization.** The UVvis spectra showed broad charge-transfer<sup>20,21</sup> bands at  $\lambda_{\text{max}}$  ~ 563 and 524 nm, and the FTIR spectra exhibited characteristic<sup>20</sup> arene- $\text{NO}^+$  stretching at  $\nu = 1923$  and  $1955 \text{ cm}^{-1}$  for **7** and **8**, respectively. The  $^1\text{H}$  NMR spectra of **7** and **8** exhibited new sets of the calixarene signals as well (Figure 5). In particular, aromatic CH protons of guest-free **1** were seen as a singlet at 6.76 ppm. In nitrosonium complex **7**, these were transformed into a singlet at 6.99 ppm. The methylene bridge  $\text{CH}_2$  protons of **1** were recorded as doublets at 4.41 and 3.12 ppm ( $J = 12.5$  Hz). In complex **7**, these were seen as doublets at 4.39 and 3.44 ppm ( $J = 13$  Hz). The aromatic protons of free **2** were seen as a doublet and a triplet, 2:1, at 6.92 and 6.68 ppm, respectively ( $J = 7.5$  Hz). In nitrosonium complex **8**, these were transformed into a triplet and a doublet, 1:2, at 7.17 and 7.08 ppm, respectively ( $J = 7.5$  Hz). The methylene bridge  $\text{CH}_2$  and  $\text{OCH}_2$  protons of **2** were seen as a singlet and a triplet, 1:1, at 3.62 and 3.54 ( $J = 7.5$  Hz), respectively. In complex **8**, these were transformed into a singlet and a triplet, 1:1, at 3.60 and 3.87 ( $J = 7.5$  Hz), respectively. Elemental analysis of extremely moisture sensitive and thermally unstable **7** and **8** proved to be difficult but reproducibly showed the CHN ratios corresponding to the presence of *only one*  $\text{NO}^+$  cation in both structures.

Independent structural evidence came from the complexation experiments between calixarenes **1** and **2** and commercially available  $\text{NO}^+\text{SbF}_6^-$  salt (Figure 2, Figure 3). Specifically, the  $\text{CDCl}_3$  solutions of **1** and **2** were treated with  $\text{NO}^+\text{SbF}_6^-$  at 295 K and the complexation induced changes in the UVvis, FTIR and  $^1\text{H}$  NMR spectra were recorded. Under these conditions, the complexation process proved to be rather slow, however after ~20 h no starting calixarenes **1,2** were observed and

the corresponding UVvis, FTIR and  $^1\text{H}$  NMR spectra exhibited features similar to those of nitrosonium complexes **7,8**. These spectral data are in agreement with the Kochi and Rathore spectral observations.<sup>9</sup>



**Figure 5.** Portions of the  $^1\text{H}$  NMR spectra (500 MHz,  $\text{CDCl}_3$ ,  $295 \pm 1$  K) of: a) calix[4]arene **1**. b) nitrosonium complex **7**; the identical spectrum was obtained upon addition of  $\text{NO}^+\text{SbF}_6^-$  to **1**. c) calix[4]arene **2**. d) nitrosonium complex **8**; the identical spectrum was obtained upon addition of  $\text{NO}^+\text{SbF}_6^-$  to **2**. The residual  $\text{CHCl}_3$  signals are marked “•”.

Analogously, a nitrosonium complex of calixarene **5** was obtained. The UVvis spectrum of dark blue complex  $5 \cdot \text{NO}^+ \text{SbF}_6^-$  showed broad band at  $\lambda_{\text{max}} \sim 600$  nm, and the FTIR spectrum exhibited characteristic<sup>20</sup> arene- $\text{NO}^+$  stretching at  $1876 \text{ cm}^{-1}$ . The  $^1\text{H}$  NMR spectrum of  $5 \cdot \text{NO}^+ \text{SbF}_6^-$  is different from **5** as well. For example, the methylene bridge  $\text{CH}_2$  and both  $\text{OCH}_2$  protons of **5** were seen as a singlet and two triplets, 1:1:1, at 3.62, 3.83 ( $J = 7 \text{ Hz}$ ), and 3.35 ppm ( $J = 7 \text{ Hz}$ ), respectively. In complex  $5 \cdot \text{NO}^+ \text{SbF}_6^-$ , these were observed at 3.44, 3.93 ( $J = 7.5 \text{ Hz}$ ), and 3.76 ppm ( $J = 7.5 \text{ Hz}$ ), respectively.

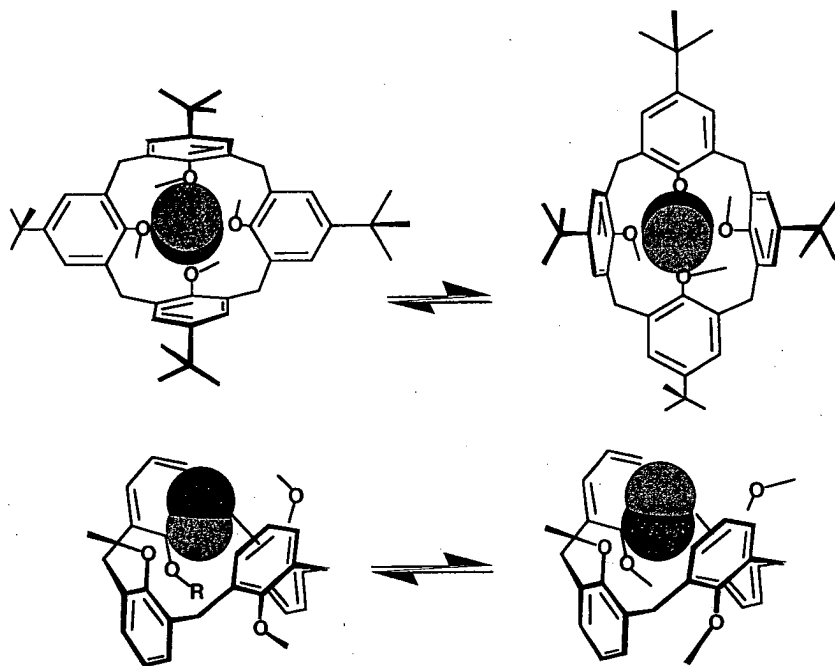
The association constants for the above complexes were too high to be measured by the  $^1\text{H}$  NMR technique. Even slight excess of  $\text{NO}^+ \text{SbF}_6^-$  results in the complete complex formation in  $\text{CDCl}_3$ , and no free calixarenes **1**, **2**, and **5** were observed after equilibration. The  $K_{\text{ass}}$  values  $> 10^6 \text{ M}^{-1}$  ( $\Delta G^{295} > 8 \text{ kcal mol}^{-1}$ ) for the complexes were estimated, which is in agreement with the published values in  $\text{CH}_2\text{Cl}_2$ .<sup>9</sup> While complexes  $1 \cdot \text{NO}^+ \text{SbF}_6^-$  and  $2 \cdot \text{NO}^+ \text{SbF}_6^-$  formed slowly, over  $\sim 20$  hrs, it took only few minutes to form complex  $5 \cdot \text{NO}^+ \text{SbF}_6^-$ . Moreover, highly electrophilic  $\text{NO}^+$  tends to further react with  $5 \cdot \text{NO}^+ \text{SbF}_6^-$ , and unidentified impurities were seen in the NMR spectrum already after several minutes. Unlike complexes  $1 \cdot \text{NO}^+ \text{SbF}_6^-$  and  $2 \cdot \text{NO}^+ \text{SbF}_6^-$ , which are chemically stable for weeks, complex  $5 \cdot \text{NO}^+ \text{SbF}_6^-$  decomposes within a day ( $^1\text{H}$  NMR).<sup>19</sup>

Addition of  $\text{H}_2\text{O}$  or  $\text{MeOH}$  to the freshly prepared  $\text{CHCl}_3$  solutions of **7** and **8** and the nitrosonium complexes prepared from **1**, **2** and **5** and  $\text{NO}^+ \text{SbF}_6^-$ , resulted in the complete complex dissociation and recovery of calixarenes **1**, **2** and **5** (preparative TLC, UVvis,  $^1\text{H}$  NMR).

We subsequently reexamined the reaction between **1** and **2** and  $\text{NO}_2$ , in the absence of  $\text{SnCl}_4$ . As excess  $\text{NO}_2$  was passed through the solution of **1**, nitrosonium complex  $[1 \cdot \text{NO}^+] \text{NO}_3^-$  was clearly seen (UVvis,  $^1\text{H}$  NMR), along with the mixture of nitration products. For **2**, no signals for

nitrosonium complex  $[2 \cdot \text{NO}^+]\text{NO}_3^-$  were seen.<sup>22</sup> Apparently, while formed these nitrosonium species quickly react with an excess  $\text{NO}_2$ . Overall, both reactions subsequently yield *p*-nitrated calixarenes.

Summarizing, reactions between  $\text{NO}_2/\text{N}_2\text{O}_4$  and *O*-alkylated calix[4]arenes proceed via the  $\text{NO}^+$  encapsulation. Calix[4]arene-nitrosonium complexes can be significantly stabilized by Lewis acids.



**Figure 6.** Host-guest dynamics in calix[4]arene- $\text{NO}^+$  complexes.

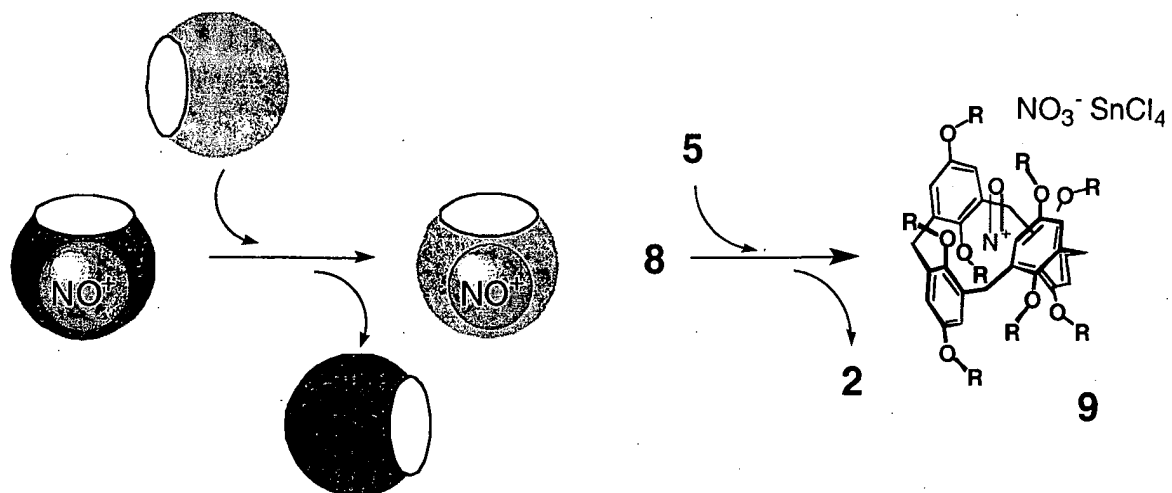
**Host-Guest Dynamics.** As evident from the  $^1\text{H}$  NMR data, the  $\text{NO}^+$  exchange in and out of the cavity is slow on the NMR time scale. For example, in the titration experiments between calixarenes **1** and **2** and  $\text{NO}^+\text{SbF}_6^-$ , both free and complexed species can be observed separately.<sup>23</sup> This is typical for the host-guest complexes with high  $K_{\text{ass}} > 10^6 \text{ M}^{-1}$  values. On the other hand, the  $\text{NO}^+$  guest, with the van der Waals dimensions  $< 2\text{\AA}$ ,<sup>20</sup> freely migrates within the cavity at room temperatures (Figure 6). Indeed, the  $^1\text{H}$  NMR spectra of complexes **7-9** possess the same symmetry

as guest-free calixarenes **1**, **2**, and **5**, which in principle should be reduced upon complexation with nonsymmetrical  $\text{NO}^+$ .

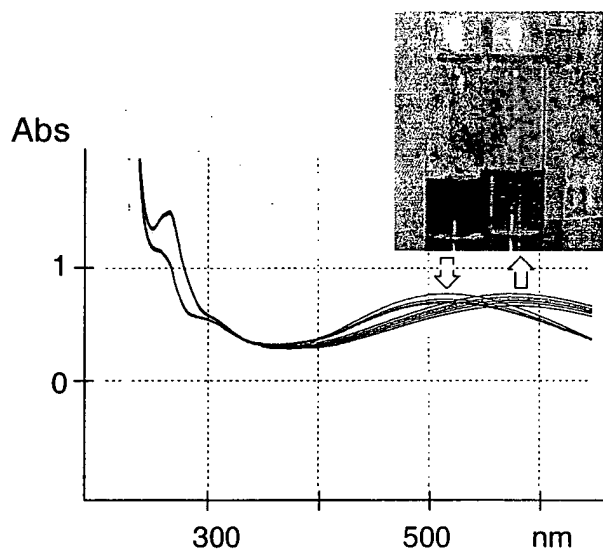
*Cone* calix[4]arene complex **7** should have a pinched,  $C_{2v}$  symmetrical conformation, since only two opposite, cofacial aromatic rings trap  $\text{NO}^+$ . Instead, the observed at room temperature NMR spectrum exhibits a  $C_{4v}$  symmetry, indicating a fast on the NMR time scale exchange between two  $C_{2v}$  structures. *1,3-Alternate* calix[4]arene complexes **8** and **9** should exhibit a  $C_{2v}$  symmetry, with two different top and bottom halves of the skeleton. Instead, the apparent at room temperature symmetry is  $S_4$ , with equal top and bottom halves.<sup>24</sup>

At the same, the complexation process is reversible, and the  $\text{NO}^+$  guest can still leave the calixarene cavity. Addition of  $\text{H}_2\text{O}$  to the freshly prepared  $\text{CHCl}_3$  solutions of **7-9** resulted in the complete dissociation and recovery of calixarenes **1,2** and **5**. Interestingly, complex **8** bleached within seconds, but it took several minutes to decompose complex **7**.<sup>25</sup> We propose, that the kinetics is responsible. Apparently, *t*-Bu groups at the upper rim of the latter complex pose significant steric hindrances and protect the encapsulated  $\text{NO}^+$  species from the entering  $\text{H}_2\text{O}$ . Such stability of the arene- $\text{NO}^+$  complex is without precedent.<sup>20</sup>

On the other hand,  $\text{NO}^+$  guest can be transferred from one calixarene container to another (Figure 7). Calixarene **5** was specifically designed to promote such transfer from the preformed complex **8**. Four additional, electron donating  $\text{O}(\text{CH}_2)_5\text{CH}_3$  groups were introduced in *p*-positions to the initial set of  $\text{O}(\text{CH}_2)_5\text{CH}_3$  groups. This makes cavity **5** significantly more  $\pi$ -electron rich and dramatically increases its affinity towards positively charged  $\text{NO}^+$ .



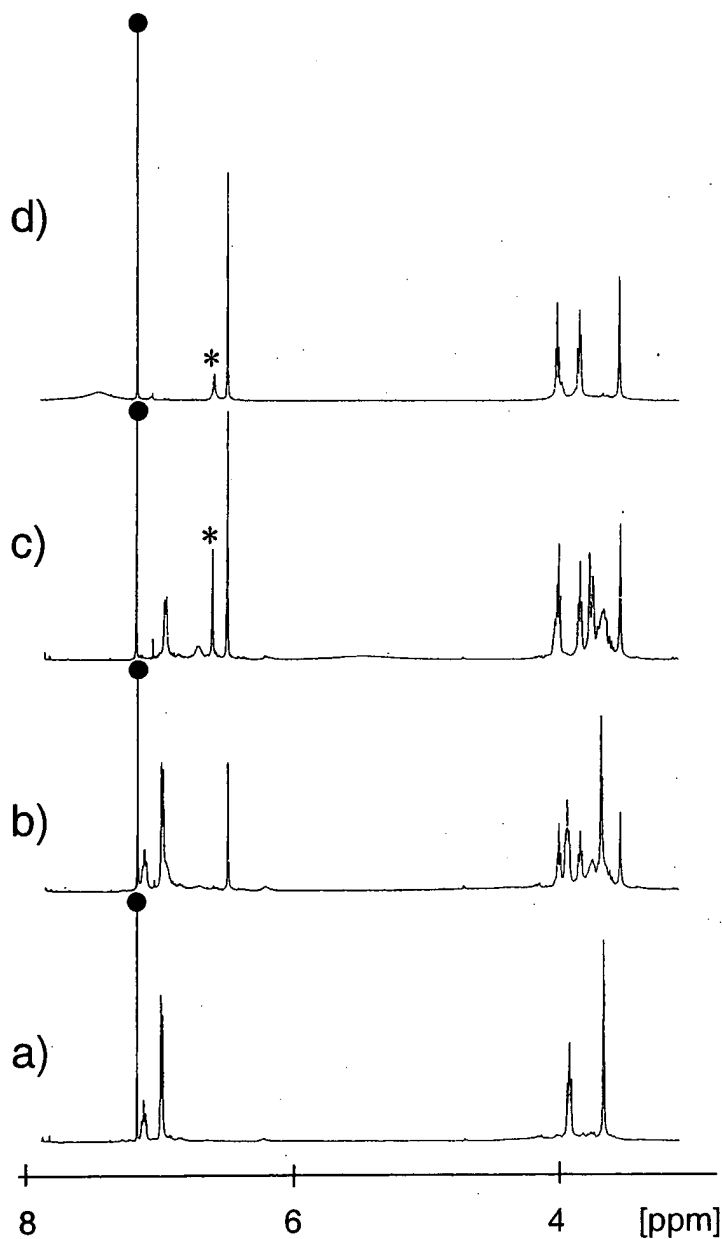
**Figure 7.** Top:  $\text{NO}^+$  transfer between calixarene containers, a cartoon representation. Bottom: formation of complex 9 from complex 8.



**Figure 8.** Nitrosonium transfer experiment. Portions of the UVvis spectra ( $[8] = [5] = 10^{-6}$  M,  $\text{CHCl}_3$ ,  $295 \pm 1$  K). Band at  $\lambda_{\text{max}} \sim 524$  nm belongs to nitrosonium complex 8, band at  $\lambda_{\text{max}} \sim 600$  nm is assigned to complex 9. Visually, the exchange results in a color change from purple to blue.

For the exchange experiments, we obtained **8** by treating calixarene **2** with 3 equivalents  $\text{NO}_2$  and 1 eq  $\text{SnCl}_4$  in  $\text{CHCl}_3$ . Further, complex **8** and “empty” host **5** were mixed in a 1:1 ratio at 295 K in dry chloroform, and the UVvis and  $^1\text{H}$  NMR spectra were recorded over two hours. Due to the

strong affinity of **2** towards  $\text{NO}^+$ , the guest presence outside the cavity, in a bulk solution, was considered negligible, and the only source of  $\text{NO}^+$  was **8**.



**Figure 9.** Portions of the  $^1\text{H}$  NMR spectra (500 MHz,  $\text{CDCl}_3$ ,  $295 \pm 1$  K) of: a) nitrosonium complex **8**, obtained from **2**,  $\text{NO}_2$  and  $\text{SnCl}_4$ . b) mixture of complex **8** and calixarene **5** after 20 min; ~30% conversion to **9**. c) the same mixture after 1 h; complex **9** is formed with >95% conversion. d) nitrosonium complex  $\mathbf{5} \cdot \text{NO}^+\text{SbF}_6^-$ , independently obtained from **5** and  $\text{NO}^+\text{SbF}_6^-$ . The residual  $\text{CHCl}_3$  signals are marked as before, the decomposition products of **5** are marked “\*”.

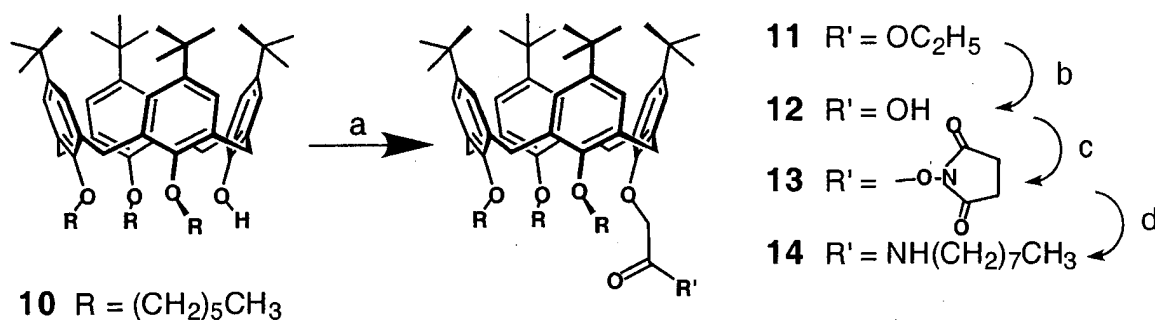
Initially, the  $^1\text{H}$  NMR spectrum exhibited only sets of signals for **8** and free calixarene **5**, and the corresponding UVvis spectrum showed only the characteristic absorption for charge-transfer in **8**. Within minutes however, the guest transfer was clearly detected. The band at  $\lambda_{\text{max}} \sim 524$  nm, assigned to complex **8**, systematically decreased and a new band at  $\lambda_{\text{max}} \sim 600$  nm, corresponding to complex **9**, appeared.

The nitrosonium transfer can even be observed visually. The purple solution of **8** in  $\text{CHCl}_3$  turns blue upon addition of calixarene **5** (Figure 8). When followed by  $^1\text{H}$  NMR spectroscopy, the  $\text{NO}^+$  exchange resulted in clean transformation of the spectra from mixture **8** + **5** to mixture **2** + **9** (Figure 9). For example, the methylene bridge  $\text{CH}_2$  and  $\text{OCH}_2$  protons of **8**, seen as a singlet and a triplet, 1:1, at 3.60 and 3.87 ppm ( $J = 7.5$  Hz), slowly decrease in intensity. Instead, two  $\text{OCH}_2$  triplets at 3.93 and 3.76 ppm ( $J = 7.5$  Hz) and the methylene bridge  $\text{CH}_2$  singlet at 3.44 ppm appear and grow. These were assigned to complex **9** and confirmed in the series of independent experiments between **5** and  $\text{NO}^+\text{SbF}_6^-$ . Signals for “empty” calixarene **2** also appear, although slightly shifted due to the presence of  $\text{SnCl}_4$ , and signals for **8** disappear. Within an hour the nitrosonium transfer was completed; both the  $^1\text{H}$  NMR and UVvis spectra exhibited only the signals of complex **9** and free calixarene **2**. No traces of initial complex **8** were detected. To our knowledge, this is the first case of a quantitative guest transfer between two different molecular containers.<sup>26</sup> Such behavior has a potential for information storage and processing since the color can be switched between two distinguishable states.

**Functionalized Silica Gel.** Presented here calix[4]arene- $\text{NO}_2$  interactions *a)* are reversible, *b)* result in dramatic color changes, and *c)* are unique and *specific* for  $\text{NO}_2$ , which should guaranty its detection in the presence of such gases as  $\text{H}_2\text{O}$ ,  $\text{O}_2$ ,  $\text{HCl}$ ,  $\text{HBr}$ ,  $\text{SO}_x$ ,  $\text{NH}_3$ , and even oxygen-free  $\text{NO}$ . Indeed, *none* of these vapors/gases undergoes such interactions/reactions with calixarenes!

Current NO<sub>2</sub> sensors are mostly electrochemical and monitor changes of potential upon exposure metal surfaces to NO<sub>2</sub>.<sup>27</sup> In many cases however, other vapors - H<sub>2</sub>O, O<sub>2</sub>, HCl, HBr, SO<sub>x</sub>, and NH<sub>3</sub> significantly influence the detection selectivity and therefore sensitivity. Optical sensors, which are based on coloration reaction between NO<sub>2</sub> and certain organic compounds, are more selective as the reactions are specific.<sup>28</sup> At the same time, reversibility of such sensing processes is not easy to achieve.

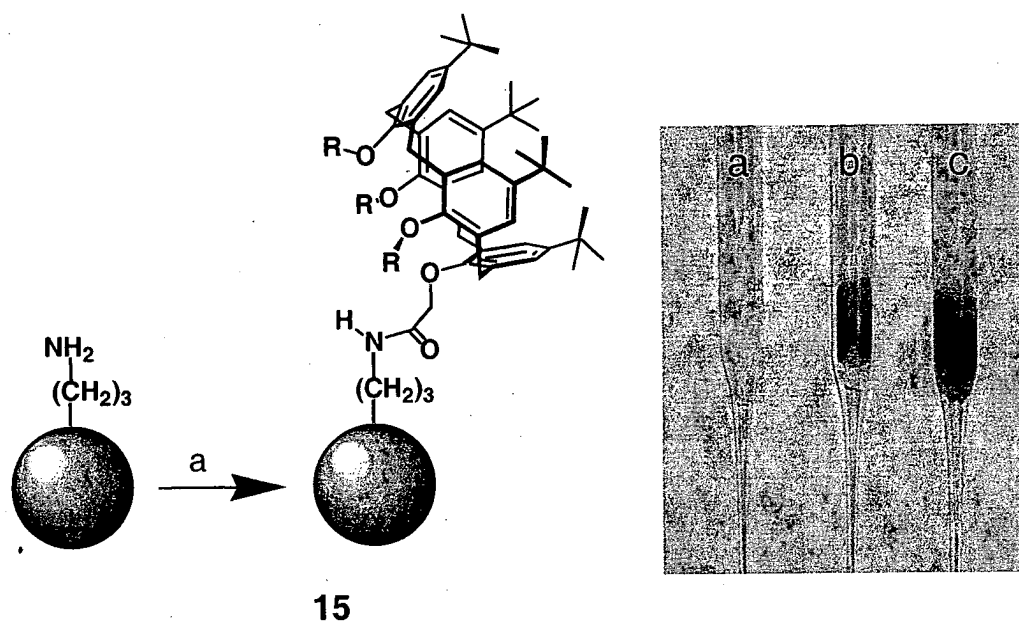
For potential application in sensing technology, receptor molecules must not only be synthetically available, but also readily immobilizable on larger (macro)molecules, solid supports or surfaces. A wide variety of polymers and nanomaterials are now commercially available. Here, we used 3-aminopropylated silica gel from Aldrich and functionalized it with calixarene modules. As follows from molecular modeling, calix[4]arene fragments are ~10 x 10 Å in their dimensions, so their attachment via *lower* rim should guaranty the proper configuration of the *upper* rim to sufficiently respond to the presence of the gas analyte.



**Scheme 3.** a) BrCH<sub>2</sub>C(O)OC<sub>2</sub>H<sub>5</sub>, Na<sub>2</sub>CO<sub>3</sub>, MeCN, 80 °C, 12 h, 89 %. b) KOH, THF-H<sub>2</sub>O, 100 °C, 12 h, then aq HCl, >95%. c) *N*-hydroxy succinimide, DCC, DMAP, THF, rt, 12 h, 83%. d) CH<sub>3</sub>(CH<sub>2</sub>)<sub>7</sub>-NH<sub>2</sub>, Et<sub>3</sub>N, THF, rt, 12 h, 65%.

Synthetically, tris-*O*-substituted calixarene **10**, prepared by selective alkylation of the parent calix[4]arene with *n*-hexylbromide and BaO/Ba(OH)<sub>2</sub><sup>29</sup> in DMF (69%), was further alkylated with ethyl bromoacetate to afford derivative **11** (Na<sub>2</sub>CO<sub>3</sub>, MeCN, 89%) (Scheme 3). This was hydrolyzed with KOH in THF-H<sub>2</sub>O mixture, resulting calixarene acid **12** in a quantitative yield.

Acid **12** was further activated with *N*-bromosuccinimide (DCC, DMAP, THF) to afford active ester **13** (83%). Compound **13** readily reacts with amines. Thus, amide **14** was prepared from **13** and *n*-octylamine (Et<sub>3</sub>N, THF, 65%) and used for control experiments. Analogously, ester **13** was coupled to 3-aminopropyl-functionalized silica gel in THF in the presence of Et<sub>3</sub>N to afford material **15** (Figure 10). The presence of a calix[4]arene fragment in **15** was confirmed by the FTIR analysis in KBr disks:  $\nu(\text{CH}) \sim 2960 \text{ cm}^{-1}$  and  $\nu(\text{C=O}) \sim 1650 \text{ cm}^{-1}$  were recorded, which are similar to the stretching of model calixarene amide **14**:  $\nu(\text{CH}) = 2964 \text{ cm}^{-1}$  and  $\nu(\text{C=O}) = 1680 \text{ cm}^{-1}$ . From the CHN analysis, only  $\sim 17\%$  calixarene loading was achieved, which may be due to the steric bulkiness of the calixarene fragment.



**Figure 10.** Left: preparation of calix[4]arene functionalized silica gel **15**: a) Et<sub>3</sub>N, THF, rt, 12 h. Right: NO<sub>2</sub> entrapment “chromatography” experiments. The columns were prepared as follows: a) loaded with starting aminopropyl functionalized silica gel; b) loaded with dry silica gel **15**; c) loaded with **15** and flashed with CHCl<sub>3</sub>. All three columns were then flashed with NO<sub>2</sub> ( $\sim 30$  seconds), and the pictures were made after  $\sim 2$ -3 minutes afterwards.

In the NO<sub>2</sub> entrapment experiments, stream of the gas was passed through Pasteur pipettes, loaded with silica gel **15** (Figure 10). In one pipette, dry silica gel **15** was loaded, and the other contained

**15** preliminary wetted with  $\text{CHCl}_3$ . Both silica gels instantly turned dark purple, indicating the  $\text{NO}^+$  complexation. The color of the wetted material appeared to be deeper and it stayed for hours. The dry material bleached within minutes. The FTIR spectrum, recorded in KBr disks, gave weak but reproducible stretch at  $\nu \sim 1920 \text{ cm}^{-1}$ , indicating the presence arene- $\text{NO}^+$  complexes. No coloration was observed for the pipette loaded with the starting, 3-aminopropylated silica gel. This once again emphasizes the role of calixarene cavities in the described processes.

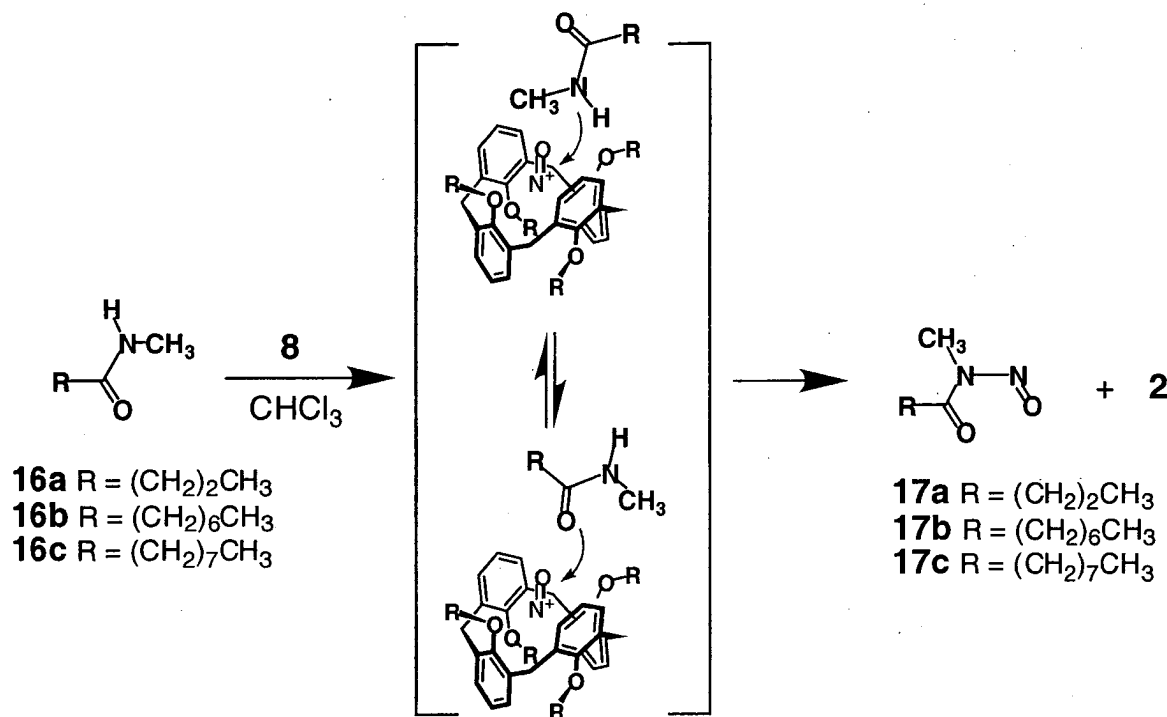
Although requiring further synthetic optimization, silica gel **15** may still be used for  $\text{NO}_2$  detection and even for purification of other nitrogen oxides, especially NO.

**Nitrosating Reagents.** The described in this paper chemistry involves chemical fixation of nitrogen dioxide ( $\text{NO}_2$ ) - its conversion to encapsulated nitrosonium ( $\text{NO}^+$ ) complexes, and subsequent  $\text{NO}^+$  transfer to the substrate. We noticed, that primary and secondary amides also reacted with **7** and **8**, which implies that these complexes may act as *nitrosating reagents*.

It is known, that reactions between  $\text{NO}^+$  generating agents (e.g.,  $\text{NOCl}$ ,  $\text{N}_2\text{O}_3$ ,  $\text{NO}_2/\text{N}_2\text{O}_4$ , nitrosonium salts, etc.) and amides and short peptides proceed via *N*-nitrosation and yield biologically important nitroso-derivatives.<sup>30</sup> Nitrosation of peptides may be used in analytical protocols of protein sequencing. More importantly however, these reactions have a biological relevance, since  $\text{NO}_x$  are widely spread atmospheric pollutants and frequently interact with biological tissues and fluids.<sup>31</sup> The corresponding reaction mechanisms typically incorporate an electrophilic attack of  $\text{NO}^+$  on a nucleophilic oxygen or nitrogen of the substrate.<sup>32</sup>

Preparatively, *1,3-alternate* based nitrosonium complex **8** was mixed with  $\text{AlkC(O)NHMe}$  **16a-c** ( $\text{Alk} = n\text{-Pr}$ ,  $n\text{-Hex}$ ,  $n\text{-Hept}$ ) in dry  $\text{CHCl}_3$  and stirred at room temperature for several hours (Figure 11). The corresponding *N*-nitrosoamides  $\text{AlkC(O)N(NO)Me}$  (**17a-c**) were formed in 30-40% yield. Under the same conditions, the *cone* calixarene complex **7** reacts very slow, and only traces of the

*N*-nitrosoamide products were detected by  $^1\text{H}$  NMR spectroscopy. Likewise with water, *t*-Bu groups at the upper rim of **7**, probably, impose steric hindrances and protect the encapsulated  $\text{NO}^+$  species from the substrate. The rate limiting formation of the nitroso intermediates, most probably, should take place within the calixarene cavity, prior to the  $\text{NO}^+$  dissociation. Once formed, these sterically bulky species leave the interior, and undergo further transformations in bulk solution.



**Figure 11.** *N*-Nitrosation of secondary amides **16a-c** with complex **8**; formation of *N*-nitrosoamides **17a-c**. Two probable pre-reactive complexes are depicted.

These transformations provide with an additional structural evidence for the discovered calixarene- $\text{NO}^+$  complexes. More important however, they open new perspectives to use calixarenes as supramolecular/encapsulated nitrosating reagents.<sup>33</sup> Here we refer to *encapsulated reagents* as to highly reactive species, reversibly entrapped within the host' cavity, which can be released to the reaction mixture under subtle control.<sup>34</sup> The cavity offers protection from the bulk environment and thus controls the reaction rates. Reactions with encapsulated reagents may occur either within the

cavity interior, or outside, upon release. As far as delicate, noncovalent forces, holding the molecule-within-molecule complex together, are concerned, temperature, solvent polarity and the *substrate-cavity size-shape fit* are the critical factors, responsible for the reagent release and for the reaction to occur. The described here complexes may be such unique encapsulated reagents for nitrosation. Supramolecular effects in these processes must be much more pronounced in *deeper* calixarenes,<sup>4c</sup> where the cavities could accommodate the reaction intermediates. We are currently preparing such structures and will report on the results in the future.

## Summary and Outlook

A novel NO<sub>2</sub> sensing and fixation process is now available, which employs simple calix[4]arenes. Calixarenes conveniently transmit the information about NO<sub>2</sub> binding via visible light signals. The described charge-transfer interactions are unique for NO<sub>2</sub> and would guaranty its detection in the presence of such gases as H<sub>2</sub>O, O<sub>2</sub>, HCl, SO<sub>x</sub>, NH<sub>3</sub>, and even NO. In principle, the resulting complexes can be used as vehicles for nitrosonium transfer and encapsulated nitrosating reagents. These findings open wider possibilities towards more sophisticated NO<sub>2</sub>/NO<sub>x</sub> sensing and storing materials. We are currently exploring all these directions.

## Experimental Section

**General.** Melting points were determined on a Mel-Temp apparatus (Laboratory Devices, Inc.) and a Buchi apparatus and are uncorrected.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded in  $\text{CDCl}_3$  at  $295 \pm 1$   $^\circ\text{C}$ , unless stated otherwise, on JEOL Eclipse 500 MHz spectrometer. Chemical shifts were measured relative to residual non-deuterated solvent resonances. FTIR spectra were recorded on a Bruker Vector 22 FTIR spectrometer. UVvis spectra were measured on a JASCO V-530 spectrophotometer. Matrix-assisted laser desorption/ionization mass spectrometry (MALDI-TOF) was performed on a Bruker Biflex I linear time-of-flight mass spectrometer operated in delayed extraction mode. Elemental analysis was performed on a Perkin-Elmer 2400 CHN analyzer. For column chromatography, Silica Gel 60 Å (Sorbent Technologies, Inc.; 200–425 mesh) was used. All experiments with moisture- or air-sensitive compounds were run in freshly distilled, anhydrous solvents under a dried nitrogen atmosphere. Molecular modeling was performed using MacroModel 7.1.<sup>17</sup>

Parent tetrahydroxycalix[4]arenes were prepared according to the published procedures.<sup>35</sup>  $\text{NO}_2$  was generated from sodium nitrate and conc.  $\text{H}_2\text{SO}_4$ . *Caution:  $\text{NO}_2$  has an irritating odor and is very toxic.*

**25,26,27,28-Tetra (*n*-hexyloxy)calix[4]arene-1,3-alternate (2).** To a suspension of 25,27,26,28-tetrahydroxycalix[4]arene<sup>35b</sup> (4.24 g, 0.01 mol) and  $\text{K}_2\text{CO}_3$  (4.2 g, 0.03 mol) in MeCN (200 mL) *n*-hexylbromide (4.2 mL, 0.03 mol) was added, and the reaction mixture was refluxed under nitrogen for 48 h. The precipitate was filtered off, and the solution was evaporated to dryness. The residue was redissolved in  $\text{CH}_2\text{Cl}_2$  (200 mL), and the solution was washed with water (3 x 150 mL) and dried over  $\text{MgSO}_4$ . After evaporation, the solid residue was treated with MeOH (200 mL) to yield

pure 5,27-bis(*n*-hexyloxy)-26,28-hydroxycalix[4]arene as a white solid (5.0 g, 84%). <sup>1</sup>H NMR: δ 8.23 (bs, 2 H), 7.06 (d, *J* = 8 Hz, 4 H), 6.91 (d, *J* = 8 Hz, 4 H), 6.73 (t, *J* = 8 Hz, 2 H), 6.65 (t, *J* = 8 Hz, 2 H), 4.32 (d, *J* = 13 Hz, 4 H), 4.00 (t, *J* = 7 Hz, 4 H), 3.37 (d, *J* = 13 Hz, 4 H), 2.1-2.0 (m, 4 H), 1.75-1.7 (m, 4 H), 1.45-1.4 (m, 8 H), 0.95 (t, *J* = 7 Hz, 6 H). To a suspension of 25,27-bis(*n*-hexyloxy)-26,28-hydroxycalix[4]arene (5.92 g, 0.01 mol) and Cs<sub>2</sub>CO<sub>3</sub> (50 g, 0.15 mol) in MeCN (300 mL) *n*-hexylbromide (5.74 mL, 0.04 mol) was added, and the reaction mixture was refluxed under nitrogen for 48 h. After cooling, the precipitate was filtered off and treated with a mixture of water (100 mL) and CH<sub>2</sub>Cl<sub>2</sub> (100 mL). The organic layer was separated, washed with water (2 x 100 mL), dried over MgSO<sub>4</sub>, and evaporated. The residue was recrystallized from MeOH-CHCl<sub>3</sub>, 10:1 to give pure **2** (3.50 g, 46%). Mp 119 °C; <sup>1</sup>H NMR: δ 6.92 (d, *J* = 7.5 Hz, 8 H), 6.68 (t, *J* = 7.5 Hz, 4 H), 3.62 (s, 8 H), 3.54 (t, *J* = 7.5 Hz, 8 H), 1.89 (m, 8 H), 1.35 (m, 24 H), 0.85 (t, *J* = 7 Hz, 12 H); MALDI-TOF MS, *m/z* 783.9 ([M+Na<sup>+</sup>], calcd for C<sub>52</sub>H<sub>72</sub>O<sub>4</sub> 783.9). Anal. Calcd for C<sub>52</sub>H<sub>72</sub>O<sub>4</sub>: C, 82.06; H, 9.53. Found: C, 81.61; H, 9.58.

**5,11,17,23-Tetrabromo-25,26,27,28-tetrakis(*n*-hexyloxy)calix[4]arene-1,3-alternate (**3**).** *N*-Bromosuccinimide (3.0 g, 0.017 mol) was added to a suspension of calixarene **2** (2.0 g, 2.6 mmol) in acetone (500 mL), and the mixture was stirred at rt for 48 h exposed to the laboratory light. The formed solid was filtered off, washed with acetone (2 x 100 mL) and used in the next step without further purification. Yield 1.5 g (53 %). <sup>1</sup>H NMR: δ 7.12 (s, 8 H), 3.56 (s, 8 H), 3.52 (t, *J* = 7.5 Hz, 8 H), 1.6-1.4 (m, 8 H), 1.4-1.3 (m, 24 H), 0.93 (t, *J* = 7 Hz, 12 H).

**5,11,17,23-Tetrahydroxy-25,26,27,28-tetrakis(*n*-hexyloxy)calix[4]arene-1,3-alternate (**4**).** To a solution of tetrabromo derivative **3** (0.9 g, 0.83 mmol) in freshly distilled over Na and oxygen-free THF (150 mL) *n*-BuLi (30 mL of 2M solution in pentane, 60 mmol) was added at -78 °C, and the

mixture was stirred at this temperature for 75 min. Trimethyl borate (14 mL, 145 mmol) was then added at  $-78^{\circ}\text{C}$ , and the mixture was allowed to warm to rt. After 5 h, the reaction mixture was cooled down again to  $-78^{\circ}\text{C}$ , and  $\text{H}_2\text{O}_2$  (15 mL of 30% aq solution) and NaOH (35 mL of 3N aq solution) was added. The resulting solution was stirred overnight at rt, after which the precipitate was filtered off. The mother liquor was cooled to  $0^{\circ}\text{C}$  and treated with  $\text{NaS}_2\text{O}_3$  (25 g), after which the mixture was filtered and the filtrate was concentrated in vacuo. The residue was treated with 5% aq HCl (100 mL), and the colorless precipitate of **4** was filtered off and washed with MeOH (50 mL). Yield 0.274 g (40%). Mp  $230^{\circ}\text{C}$ ;  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  8.39 (bs, 4 H), 6.34 (s, 8 H), 3.50 (s, 8 H), 3.02 (t,  $J = 7.5$  Hz, 8 H), 1.3-1.25 (m, 8 H), 1.25-1.1 (m, 16 H), 1.1-1.0 (m, 8 H), 0.87 (t,  $J = 7$  Hz, 12 H); MALDI-TOF MS,  $m/z$  847 ( $[\text{M}+\text{Na}^+]$ , calcd for  $\text{C}_{52}\text{H}_{72}\text{O}_8$  847).

**5,11,17,23,25,26,27,28-Octa(n-hexyloxy)calix[4]arene-1,3-alternate (5).** To a suspension of **4** (0.3 g, 0.36 mmol) and NaH (0.15 g of 60% (wt.) suspension in mineral oil, 3.6 mmol) in freshly distilled DMF (50 mL) *n*-hexylbromide (0.46 mL, 3.2 mmol) was added, and the reaction mixture was stirred at  $70^{\circ}\text{C}$  under nitrogen for 24 h. The precipitate was filtered off, and the mother liquor was treated with a mixture of crushed ice (50 g), water (50 mL) and  $\text{CH}_2\text{Cl}_2$  (100 mL). The organic layer was separated, washed with water (2 x 100 mL), dried over  $\text{MgSO}_4$  and evaporated. The residue was recrystallized from MeOH- $\text{CHCl}_3$ , 10:1 to yield calixarene **5** (0.35 g, 85 %). Mp  $111^{\circ}\text{C}$ ,  $^1\text{H}$  NMR:  $\delta$  6.55 (s, 8 H), 3.83 (t,  $J = 7$  Hz, 8 H), 3.62 (s, 8 H), 3.35 (t,  $J = 7$  Hz, 8 H), 1.7 (m, 16 H), 1.4-1.2 (m, 48 H), 0.89 (t,  $J = 7$  Hz, 24 H);  $^{13}\text{C}$  NMR:  $\delta$  153.6, 150.7, 134.4, 115.2, 71.6, 68.1, 37.8, 32.3, 31.8, 29.8, 26.0, 25.9, 22.9, 22.7, 14.3, 14.1; MALDI-TOF MS,  $m/z$  1182 ( $[\text{M}+\text{Na}^+]$ , calcd for  $\text{C}_{76}\text{H}_{120}\text{O}_8$  1183).

**Tetrakis(*O*-*n*-hexyloxy)cyclophane (6).** NaH (0.11 g of 60% suspension in mineral oil, 2.7 mmol) was added to the solution of Pappalardo's cyclophane<sup>15,16</sup> (0.2 g, 0.34 mmol) in freshly distilled DMF (20 mL), and the mixture was stirred under nitrogen for 30 min. *n*-Hexylbromide (0.3 mL, 2.04 mmol) was then added, and the reaction mixture was stirred at 70 °C for 3 days. The precipitate was collected and dissolved in CH<sub>2</sub>Cl<sub>2</sub> (20 mL). The solution was washed with water (3 x 20 mL), dried over MgSO<sub>4</sub> and evaporated. The residue was recrystallised from MeOH-CHCl<sub>3</sub> to afford **6** as a white powder. Yield 0.157 g (50 %); <sup>1</sup>H NMR: δ 3.89 (s, 8 H), 3.58 (t, *J* = 7 Hz, 8 H), 2.30 (s, 24 H), 1.8-1.7 (m, 8 H), 1.6-1.5 (m, 16 H), 1.4-1.35 (m, 8 H), 1.07 (s, 12 H), 0.91 (t, *J* = 7 Hz, 12 H); <sup>13</sup>C NMR: δ 153.9, 138.4, 131.4, 126.7, 73.2, 32.8, 32.0, 30.4, 26.0, 22.8, 17.7, 14.2, 13.7. Anal. Calcd for C<sub>64</sub>H<sub>96</sub>O<sub>4</sub>: C 82.70; H 10.41. Found: C, 82.37; H, 10.25.

**Preparation of Calix[4]arene-Nitrosonium Complexes.** In a typical procedure, solution of calixarene **1** (1 eq) in dry, freshly distilled CHCl<sub>3</sub> was mixed with the stock solution of NO<sub>2</sub> (2 - 3 eq) in CHCl<sub>3</sub> and SnCl<sub>4</sub> (1.5 eq) at rt. After 1 h, complex **7** was precipitated upon addition of hexane, filtered off, washed with hexane (2 x), and dried in vacuo. <sup>1</sup>H NMR: δ 6.99 (s, 8 H), 4.39 (d, *J* = 13 Hz, 4 H), 4.02 (t, *J* = 7.5 Hz, 8 H), 3.44 (d, *J* = 13 Hz, 4 H), 2.0-1.9 (m, 8 H), 1.5-1.3 (m, 24 H), 0.93 (t, *J* = 7 Hz, 12 H); UVvis (CHCl<sub>3</sub>): λ<sub>max</sub> 563; FTIR (CDCl<sub>3</sub>): ν 1923(NO<sup>+</sup>), 1461, 1298, 1047 (NO<sub>3</sub><sup>-</sup>); Anal. Calcd for C<sub>68</sub>H<sub>104</sub>O<sub>4</sub>•NO<sup>+</sup>NO<sub>3</sub><sup>-</sup>•1.8SnCl<sub>4</sub>: C, 52.81; N, 1.81; H, 6.78. Found: C, 52.60; N, 1.67; H, 7.55. Complex **8** was obtained analogously: <sup>1</sup>H NMR: δ 7.17 (t, *J* = 7.5 Hz, 4 H), 7.08 (d, *J* = 7.5 Hz, 8 H), 3.87 (t, *J* = 7.5 Hz, 8 H), 3.60 (s, 8 H), 1.9-1.8 (m, 8 H), 1.4-1.3 (m, 24 H), 0.93 (t, *J* = 7 Hz, 12 H); UVvis (CHCl<sub>3</sub>): λ<sub>max</sub> 524 nm; FTIR (CDCl<sub>3</sub>): ν 1955 (NO<sup>+</sup>), 1438, 1246, 1091 (NO<sub>3</sub><sup>-</sup>); Anal. Calcd for C<sub>52</sub>H<sub>72</sub>O<sub>4</sub>•NO<sup>+</sup>NO<sub>3</sub><sup>-</sup>•1.5SnCl<sub>4</sub>: C, 50.21; N, 2.25; H, 5.83. Found: C, 50.23; N, 1.82; H, 5.99. Complex **9** cannot be prepared using this protocol; only dealkylation/oxidation products were detected.

Alternatively, calix[4]arene-nitrosonium complexes were obtained upon mixing **1,2** or **5** with an excess  $\text{NO}^+\text{SbF}_6^-$  in dry  $\text{CHCl}_3$ . Complexes  $\mathbf{1}\cdot\text{NO}^+\text{SbF}_6^-$  and  $\mathbf{2}\cdot\text{NO}^+\text{SbF}_6^-$  formed within 20 h. The UVvis, FTIR and  $^1\text{H}$  NMR spectra are identical with the respective complexes **7** and **8**. Complex  $\mathbf{5}\cdot\text{NO}^+\text{SbF}_6^-$  formed immediately upon mixing:  $^1\text{H}$  NMR:  $\delta$  6.54 (s, 8 H), 3.93 (t,  $J = 7.5$  Hz, 8 H), 3.76 (t,  $J = 7.5$  Hz, 8 H), 3.44 (s, 8 H), 1.8-1.75 (m, 8 H), 1.9-1.8 (m, 8 H), 1.5-1.2 (m, 48 H), 0.95 (t,  $J = 7$  Hz, 12 H), 0.89 (t,  $J = 7.5$  Hz, 12 H); UVvis ( $\text{CHCl}_3$ ):  $\lambda_{\text{max}}$  600; FTIR ( $\text{CDCl}_3$ ):  $\nu(\text{NO}^+)$  1875.

**25-Hydroxy-26,27,28-trihexyloxy-*p*-tert-butylcalix[4]arene (10).** A mixture of 25,26,27,28-tetrahydroxy-*p*-tert-butylcalix[4]arene<sup>35a</sup> (4.0g, 6.2 mmol), freshly distilled anhydrous DMF (80 mL),  $\text{Ba}(\text{OH})_2\cdot 8\text{H}_2\text{O}$  (6.8g, 21.6 mmol), and BaO (6.36g, 41.5 mmol) was stirred at rt for 15 min. *n*-Hexylbromide (21 mL, 184 mmol) was added, and the suspension was stirred at rt for another 12 h. The mixture was diluted with water (100 mL), and the product was extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 100 mL). The organic layer was washed with water (2 x 100 mL), dried over  $\text{Na}_2\text{SO}_4$  and evaporated under reduced pressure. The residue was recrystallized from MeOH to give pure **10** as a white solid. Yield 69%; mp 134-136 °C;  $^1\text{H}$  NMR:  $\delta$  7.11 (s, 2 H), 7.03(s, 2 H), 6.51 (d,  $J = 2.3$  Hz, 2 H), 6.49 (d,  $J = 2.3$  Hz, 2 H), 5.72 (s, 1 H), 4.36 (d,  $J = 13$  Hz, 2 H), 4.32 (d,  $J = 13$  Hz, 2 H), 3.89 (t,  $J = 8$  Hz, 2 H), 3.78 (t,  $J = 8$  Hz, 4 H), 3.22 (d,  $J = 13$  Hz, 2 H), 3.16 (d,  $J = 13$  Hz, 2 H), 2.3-2.2 (m, 2 H), 2.0-1.8 (m, 4 H), 1.4-1.3 (m, 18 H), 1.32 (s, 9 H), 1.31 (s, 9 H), 0.92 (t,  $J = 7$  Hz, 3H), 0.90 (m, 6 H), 0.81 (s, 18 H).

**25-[(Ethoxycarbonyl)methoxy]-26,27,28-trihexyloxy-*p*-tert-butylcalix[4]arene (11).** A mixture of calix[4]arene **10** (5.0g, 5.6 mmol) and  $\text{Na}_2\text{CO}_3$  (10.0g, 94 mmol) in  $\text{CH}_3\text{CN}$  (150 mL) was refluxed for 15 min, after which ethyl bromoacetate (10mL, 90 mmol) was added, and the reflux

continued for 12 h. The inorganic salts were filtered, and the solvent was evaporated. The residue was dissolved in  $\text{CH}_2\text{Cl}_2$  (100 mL) and washed with water (3 x 50 mL). The solvent was evaporated, and the product was recrystallized from MeOH. Yield 89%; mp 121-123 °C;  $^1\text{H}$  NMR:  $\delta$  6.91(s, 2 H), 6.90 (s, 2 H), 6.63 (d,  $J$  = 2 Hz, 2 H), 6.61 (d,  $J$  = 2 Hz, 2 H), 4.86 (s, 2 H), 4.66 (d,  $J$  = 12.5 Hz, 2 H), 4.38 (d,  $J$  = 12.5 Hz, 2 H), 4.18 (q,  $J$  = 7 Hz, 2 H), 3.83 (t,  $J$  = 8 Hz, 4 H), 3.75 (t,  $J$  = 8 Hz, 2 H), 3.15 (d,  $J$  = 12.5 Hz, 2 H), 3.10 (d,  $J$  = 12.5 Hz, 2 H), 2.2-2.1 (m, 2 H), 2.0-1.9 (m, 4 H), 1.4-1.3 (m, 18 H), 1.27 (t,  $J$  = 7 Hz, 3 H), 1.18 (s, 9 H), 1.17 (s, 9 H), 0.96 (s, 18 H), 0.9-0.8 (m, 9 H).

**25-(Carbomethoxy)-26,27,28-trihexyloxy-*p*-tert-butylcalix[4]arene (12).** A mixture of **11** (2.0 g 2 mmol), THF- $\text{H}_2\text{O}$ , 5:1 (100 mL) and KOH (1.0 g, 17.8 mmol) was refluxed for 12 h. The pH was adjusted to 4 with aq 2 M HCl. The product was extracted with  $\text{CH}_2\text{Cl}_2$  (2 x 50 mL), and the organic layer was dried over  $\text{Na}_2\text{SO}_4$  and evaporated to give **12** as a white solid. Yield >95%; mp 136-137 °C;  $^1\text{H}$  NMR:  $\delta$  11.28 (s, 1 H), 7.16 (s, 2 H), 7.14 (s, 2 H), 6.59 (d,  $J$  = 2.5 Hz, 2 H), 6.49 (d,  $J$  = 2.5 Hz, 2 H), 4.67 (s, 2 H), 4.45 (d,  $J$  = 12 Hz, 2 H), 4.23 (d,  $J$  = 12 Hz, 2 H), 4.08 (t,  $J$  = 7 Hz, 2 H), 3.8-3.7 (m, 4H), 3.24 (d,  $J$  = 12 Hz, 2 H), 3.16 (d,  $J$  = 12 Hz, 2 H), 1.95-1.8 (m, 6 H), 1.45-1.2 (m, 18 H), 0.90 (t,  $J$  = 7 Hz, 9 H), 0.83 (s, 18 H); MALDI-TOF MS,  $m/z$  959.2 ( $\text{M}^+$ , calcd for  $\text{C}_{64}\text{H}_{94}\text{O}_6$  960.4). Anal. Calcd for  $\text{C}_{64}\text{H}_{94}\text{O}_6$ : C 80.12; H 9.88. Found: C, 80.27; H, 9.88.

***N*-Succinimide Ester of 25-(Carbomethoxy)-26,27,28-trihexyloxy-*p*-tert-butylcalix[4]arene (13).** A suspension of **12** (1.0g, 1.05 mmol), *N*-hydroxy succinimide (1.0g, 8.70 mmol), DCC (210 mg 1.05 mmol) and DMAP (40 mg, 0.32 mmol) in THF (50 mL) was stirred at rt for 12 h under nitrogen. After filtration, the solvent was evaporated, and the residue was redissolved in hexane (50 mL) and filtered again. The hexane solution was evaporated and the residue was purified by column chromatography ( $\text{CH}_2\text{Cl}_2$ -hexane, 1:1) to afford **13** as a white solid. Yield 83%; mp 75-78 °C;  $^1\text{H}$

NMR:  $\delta$  6.95 (s, 2 H), 6.92 (s, 2 H), 6.62 (d,  $J = 2.5$  Hz, 2 H), 6.56 (d,  $J = 2.5$  Hz, 2 H), 5.28 (s, 2 H), 4.56 (d,  $J = 13$  Hz, 2 H), 4.41 (d,  $J = 13$  Hz, 2 H), 3.89 (t,  $J = 8$  Hz, 2 H), 3.79 (t,  $J = 8$  Hz, 2 H), 3.75 (t,  $J = 8$  Hz, 2 H), 3.18 (d,  $J = 13$  Hz, 2 H), 3.12 (d,  $J = 13$  Hz, 2 H), 2.82 (s, 4 H), 2.15-2.1 (m, 2 H), 1.95-1.85 (m, 4 H), 1.45-1.35 (m, 18 H), 1.20, 1.19 (2 x s, 18 H), 0.93 (s, 18 H), 0.9-0.8 (m, 9 H). Ester **13** appeared to be relatively unstable, and attempts to obtain the MALDI-TOF and/or CHN analytical data failed. The structure of **13** was confirmed through its transformation to calixarene amide **14**.

**25-[(*n*-Octylcarbamoylmethoxy)-26,27,28-trihexyloxy-*p*-*tert*-butylcalix[4]arene (14).** To the solution of ester **13** (75 mg, 70  $\mu$ mol) in THF (10 mL), *n*-octylamine (18 mg, 0.14 mmol) and Et<sub>3</sub>N (70 mg, 0.7 mmol) were added, and the reaction mixture was stirred at rt for 12 h. The precipitate was filtered off, and the solution was evaporated. The residue was redissolved in CH<sub>2</sub>Cl<sub>2</sub> (20 mL), washed with 2 M aq HCl (2 x 5 mL) and water (5 mL), and dried over Na<sub>2</sub>SO<sub>4</sub>. The organic layer was then evaporated and the residue was recrystallized from CH<sub>3</sub>CN to afford **14** as a white solid. Yield 65%; <sup>1</sup>H NMR:  $\delta$  8.43 (t,  $J = 6$  Hz, 1 H), 6.99 (s, 2 H), 6.97 (s, 2 H), 6.57 (s, 4 H), 4.71 (s, 2 H), 4.38, 4.35 (2 x d,  $J = 13$  Hz, 4 H), 3.9-3.7 (2 x m, 6 H), 3.42 (dt,  $J = 6$  Hz,  $J = 7$  Hz, 2 H), 3.23 (d,  $J = 13$  Hz, 2 H), 3.14 (d,  $J = 13$  Hz, 2 H), 2.0-1.8 (3 x m, 8 H), 1.5-1.3 (m, 30 H), 1.25 (s, 9 H), 1.23 (s, 9 H), 0.93 (s, 18 H), 0.95-0.85 (m, 12 H). FTIR (KBr):  $\nu$  3346 (NH), 2964, 1680 (C=O), 1537, 1473. Anal. Calcd for C<sub>72</sub>H<sub>111</sub>NO<sub>5</sub>•0.5CH<sub>3</sub>CN: C, 80.35; H, 10.39; N, 1.93. Found: C 80.02; H 10.09; N, 1.91. Compound **14** was also independently synthesized from the acid chloride of **12** (prepared with SOCl<sub>2</sub>), *n*-octylamine<sup>1</sup> and Et<sub>3</sub>N in CHCl<sub>3</sub>.

**Calix[4]arene Functionalized Silica Gel (15).** A suspension of ester **13** (100 mg, 95  $\mu$ mol), 3-aminopropyl-functionalized silica gel (Aldrich) (226 mg, 155  $\mu$ mol) and Et<sub>3</sub>N (92.9 mg, 0.92

mmol) in THF (50 mL) was stirred at rt for 12 h. The solid was filtered off, washed with CH<sub>2</sub>Cl<sub>2</sub>, MeOH, water, MeCN, and THF, and then dried under reduced pressure for 3 days. Afford white powder. FTIR (KBr):  $\nu$  3383, 2960, 1650, 1556, 1477. Anal. Found for 3-aminopropyl silica gel (0.687 meq/g, C<sub>9</sub>H<sub>23</sub>NO<sub>3</sub>Si): C, 7.42; H, 1.80; N, 1.91. Anal. Calcd for silica gel **15** (17% loading, 0.117 meq/g, C<sub>73</sub>H<sub>115</sub>NO<sub>8</sub>Si): C, 15.43; H, 2.68; N, 1.82. Found: C 15.34; H 2.97; N, 1.70.

***N*-Nitrosation of Amides by Calix[4]arene-Nitrosonium Complexes; General Procedure.**

**Caution:** *N*-Nitrosoamides are potential carcinogens and should be treated with extreme care.<sup>36</sup>

Complex **8** (1 eq) was added to the solution of amide AlkC(O)NHMe **16a-c** (1 eq) in freshly distilled CHCl<sub>3</sub>, and the reaction mixture was stirred at rt for 5 h. The solvent was evaporated, and the residue was analysed by <sup>1</sup>H NMR spectroscopy and further separated by preparative TLC. The spectral data for the obtained *N*-nitroso compounds AlkC(O)N(NO)Me **17a-c** were identical with those independently obtained from AlkC(O)NHMe and NO<sup>+</sup>SbF<sub>6</sub><sup>-</sup>, and also previously published.<sup>37</sup>

CH<sub>3</sub>(CH<sub>2</sub>)<sub>6</sub>C(O)NHCH<sub>3</sub> (**16b**): <sup>1</sup>H NMR:  $\delta$  6.13 (bs, 1 H, NH), 2.73 (d,  $J$  = 5 Hz, 3 H, N-CH<sub>3</sub>), 2.13 (t,  $J$  = 7.5 Hz, 2 H, C(O)CH<sub>2</sub>), 1.6-1.5 (m, 2 H, CH<sub>2</sub>), 1.3-1.1 (m, 8 H, CH<sub>2</sub>), 0.83 (t,  $J$  = 7.5 Hz, 3 H, CH<sub>3</sub>). CH<sub>3</sub>(CH<sub>2</sub>)<sub>6</sub>C(O)N(NO)CH<sub>3</sub> (**17b**): <sup>1</sup>H NMR:  $\delta$  3.13 (t,  $J$  = 8 Hz, 2 H, C(O)CH<sub>2</sub>), 3.03 (s, 3 H, N(NO)-CH<sub>3</sub>), 1.8-1.7 (m, 2 H, CH<sub>2</sub>), 1.4-1.2 (m, 8 H, CH<sub>2</sub>), 0.84 (t,  $J$  = 7.5 Hz, 3 H, CH<sub>3</sub>).

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## Notes and References

\* Corresponding author. E-mail: [rudkevich@uta.edu](mailto:rudkevich@uta.edu). Phone: 817 272 5245. FAX: 817 272 3808.

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- As an excess NO<sub>2</sub> was passed through the solution of **2**, no signals for nitrosonium complex [2•NO<sup>+</sup>]NO<sub>3</sub><sup>-</sup> were seen, but nitronium complex [2•NO<sub>2</sub><sup>+</sup>]NO<sub>3</sub><sup>-</sup> was detected. Complexation studies with calixarene **1** and NO<sub>2</sub><sup>+</sup>SbF<sub>6</sub><sup>-</sup> in CDCl<sub>3</sub> revealed the formation of kinetically stable complex [1•NO<sub>2</sub><sup>+</sup>]SbF<sub>6</sub><sup>-</sup>. Judging from the intense coloration, the calixarene walls, most

probably, encapsulate  $\text{NO}_2^+$ . Detailed description of observed calixarene-nitronium complexes will be published separately.

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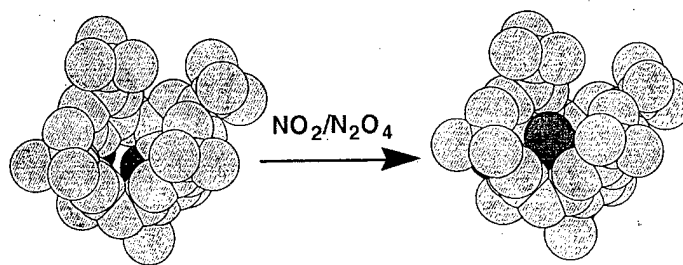
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**Sensing and Fixation of  $\text{NO}_2/\text{N}_2\text{O}_4$   
by Calix[4]Arenes**

Grigory V. Zyryanov, Yanlong Kang,  
and Dmitry M. Rudkevich\*



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